AstraZeneca

Date: APR 2 7 2004

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0117
Response to FDA Call for Comments
Draft Guidance on E2E Pharmacovigilance Planning

Dear Sir or Madam:

Reference is made to the March 30, 2004 Federal Register notice (Volume 69, Number 61, pages 16579 – 16580) announcing the request for comments on the draft guidance on E2E Pharmacovigilance Planning.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Debra N. Shiozawa, Associate Director, at (302) 886-3137.

Sincerely,

Debra N. Shiozawa for BS

Barry Sickels, Executive Director
US Regulatory Affairs
Telephone: (302) 886-5895
Fax: (302) 886-2822

DNS

Enclosure

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

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Comments from AstraZeneca on the

Draft Guidance on E2E Pharmacovigilance Planning

(Docket Number: 2004D-0117)

General Comments

- Comment 1

Overall, the document is well written, comprehensive and consistent with FDA risk management concept papers and the EU Heads of Agencies Summary Paper on risk management.

- Comment 2

Some readers found the guideline to be rather non-specific in some instances:

- **1.3 Scope** (page 3): "...a Pharmacovigilance Specification and Pharmacovigilance plan that might be submitted at the time of license application."
- **2.1 Elements of the specification** (page 4): "The elements of the Pharmacovigilance Specification that are included are only a guide."
- **3.1 Purpose** (page 5): "The plan would normally be developed by the sponsor and can be discussed with regulatory during product development..."

Equally, it was recognized that this level of non-specificity provides companies with sufficient flexibility to keep the required resources for planning and running these detailed pharmacovigilance activities tolerable.

- Comment 3

It is not clear when the PVP should be submitted? Should it be at the time of the license application (**1.3 Scope** (page 3)) or prior to approval (**3.1 Purpose** (page 5)), after submission but during the evaluation?

Draft guidance: E2E Pharmacovigilance Planning		
Section	**Page**	**Comment or proposed replacement text**
2 Pharmacovigilance Specification	3	It might be useful to state up front in the document that the PV specification and plan can either be included as a stand-alone document in Module 2 of the CTD, or that elements of the document can be incorporated into Module 2. This option is presented in this section, but might be more useful if moved to the front of the document.
2.1.1 Non-clinical	4	What does the statement "*...non-clinical safety concerns that have not been resolved by clinical data*" mean? Does it mean preclinical findings that were not confirmed in clinical investigation, or clinical findings that were not predicted by the preclinical work, or both?
2.1.2 Clinical	4	Section 2.1.2.e. has the heading "Epidemiology of the indication(s) and important **adverse events**". The use of 'adverse events' is ambiguous; what is really meant? If it is the symptoms/signs associated with the underlying disease, this could be expressed more clearly, since an adverse event is generally understood to be a medical condition occurring during exposure to a pharmaceutical product rather than an event in association with a disease being treated.
3.2.1 Structure of the Pharmacovigilance Plan	6	Use of the phrase "*Important missing information*" might pose some questions from a legal perspective. Suggest revising to read "*Ongoing and planned studies*" or "*Additional proposed studies (or work).*" This section states that a Pharmacovigilance Plan <u>should</u> contain a summary of the important identified risks etc., particularly if the Plan is a separate document from the Pharmacovigilance Specification. If the word 'should' means 'must', as it does in Swedish, it may be inappropriate to use in this manner - it could be rephrased to "*... give a reference to the Pharmacovigilance Specification or provide a summary of the following if the*

Draft guidance: E2E Pharmacovigilance Planning		
Section	**Page**	**Comment or proposed replacement text**
		Pharmacovigilance Specification and Plan are separate documents".
3.2.3 Safety action plan for specific issues	6-7	This section uses the word 'Oversight'. 'Monitoring' might be a better word, since 'oversight' can have two meanings (failure to notice vs. supervision).
3.2.4 Summary of actions to be completed, including milestones	7	The PV specification/plan will likely serve as the basis for phase IV commitments with the FDA and post-approval commitments for other health authorities. This is that will need to be considered when a sponsor prepares the plan for submission to health authorities.
Annex - Cohort study	12-13	The final sentence contains a comment regarding patient privacy and confidentiality. It has been suggested that this wording be made more prominent, perhaps by including the language at the beginning of the Annex. Although there are HIPAA exemptions where public health/safety are concerned, several of the PV methods outlined in the Annex could potentially raise HIPPA concerns.
Annex - Targeted Clinical Investigations	13-14	These studies can sometimes be extremely difficult to conduct. It can also be difficult to obtain Institutional Review Board (IRB) approval for studies intended to evaluate a previously identified risk. Some IRBs may question the value of exposing a patient to a known risk. In addition, conducting drug-drug interaction studies where a sponsor has already shown evidence of a drug interaction may also raised IRB concern. This approach is not the same as the typical drug-drug interaction studies conducted during the normal drug development process where a sponsor does not yet know if there is an interaction.